IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

ANDREA PERRY and GEORGE PERRY, both individually and as next friends of ANDREAS PERRY, a minor,	)	
Plaintiffs,	)	Civil Action No. 05-CV-5350
vs.	)	
NOVARTIS PHARMACEUTICALS CORPORATION, *et al.*,	)	
Defendants.	)	

PLAINTIFFS' OPPOSITION TO DEFENDANT'S MOTION FOR LEAVE TO FILE A REPLY BRIEF IN SUPPORT OF ITS MOTION TO EXCLUDE PLAINTIFFS' EXPERTS ON ISSUES OF MEDICAL CAUSATION

The wisdom of Local Rule 7.1(c), which generally precludes the submission of reply briefs absent prior Court permission, is revealed upon review of Novartis' instant motion. Asserting that a reply memorandum is warranted here (Def. Motion at 1), Defendant improperly raises new arguments, re-interprets (and sadly misstates) studies in ways never fathomed by its experts, and submits additional corporate and regulatory documents well beyond its opening memorandum and expert disclosures. That is not proper in reply. *Interbusiness Bank, N.A. v. First National Bank of Mifflintown*, 328 F. Supp. 2d 522, 529 (M.D. Pa. 2004).

Elsewhere, Novartis resorts to redundancy, simply re-arguing the points set forth in its opening memorandum, *e.g.*, the extensive levels of pimecrolimus found in the lymphatic system following topical exposure mean nothing (Def. Mem. at 26-27, 44), and

adverse event reports cannot alone be used to demonstrate causation (Def. Mem. at 39-42). But Defendant's desire to emphasize its initial memorandum is no basis for reply.

In the end, Local Rule 7.1 sets the proper presumption. No reply is warranted and none should be permitted.

ARGUMENT

A. The Elidel Dermal Studies Requested by FDA Are Highly Relevant and Were Properly Considered by Plaintiffs' Experts

Novartis takes exception to Dr. Smith's and Dr. Kolb's reliance on, and conclusions from, studies requested by FDA and conducted by Novartis to determine the extent to which pimecrolimus concentrates in lymphatic tissues following topical Elidel use. Def. Reply at 3-6. As a threshold matter, the studies, their relevance, and the methods employed by Dr. Smith and Dr. Kolb in examining them, were all subjects extensively described in the reports and depositions of Plaintiffs' experts. *See, e.g.,* PX 1 ¶¶ 11-12 (Smith Rpt.); PX 3 at 2 (Kolb Rpt.). Any challenge to them should have been a subject for Defendant's initial memorandum.

On the merits, Defendant's arguments fare no better. Novartis contends that Plaintiffs and their experts have misinterpreted the results of two dermal Elidel studies—the two week monkey dermal study and the one week minipig study. In particular, Defendant contends that the "authors" of the dermal monkey study (Novartis employees) concluded there was a "substantial" margin of safety with dermal use of Elidel.[1] Def.

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[1] In its Reply, Novartis variously proffers the self-serving conclusions and statements of Novartis documents analyzing otherwise negative test results, and asks the Court to accept those statements over the analysis and conclusions of Plaintiffs' experts. *See* Def. Reply at 5. Though the data from the studies are not presently disputed, the implications and conclusions from the data obviously are. Notwithstanding Novartis' contentions otherwise (Def. Reply at 3-5), Dr. Smith and Dr. Kolb are not bound by the Novartis scientists' interpretations, and may properly review Defendant's data and draw their own conclusions on it. *See, e.g., Ruff v. Ensign-Bickford*

Reply at 4. That, however, was not Novartis' conclusion with respect to the particular tissues relevant to this action. In fact, Defendant specifically questioned the existence of *any* safety margin for the draining lymph nodes and thymus—the site of Andreas Perry's lymphoma. *See* Ex. A at ELED-00986457 (PK Studies Document, Apr. 25, 2007) ("Safety Margin exists for most organs, incl[uding] lymphatic tissue, ***except possibly for local draining lymph nodes and thymus.***") (emphasis added); *id.* ("Draining lymph nodes and thymus are more exposed than various other body lymph nodes and spleen."). Plaintiffs' experts explained why no safety margin existed for these tissues: dermal application leads to lymph node and thymus concentrations of pimecrolimus sufficient to cause immunosuppression and ultimately cancer. PX 1 ¶ 102 (Smith Rpt.); PX 3 at 7 (Kolb Rpt.).

Novartis next argues that the one week dermal mini-pig study demonstrates that pimecrolimus reaches the lymph nodes and related tissues throughout the body following topical Elidel exposure by virtue of the bloodstream, not through lymphatic uptake. Def. Reply at 3. Of course, Defendant's current contention is contrary to the many pages in its opening memorandum (and even Reply) where it denies that Elidel use leads to systemic distribution of pimecrolimus through the blood. Def. Mem. at 24-27; Def. Reply at 1, 5. It is likewise contrary to the conclusions that Novartis elsewhere drew regarding these dermal studies, namely that following topical Elidel use, pimecrolimus "is taken up into, and eliminated from the lymphatic system, apparently via the draining lymph nodes." *See* Exh. A at ELED-00986457 (PK Studies Document, Apr. 25, 2007). Regardless of

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Indus., 168 F. Supp. 2d 1271, 1285 (D. Utah 2001) (expert's analysis of study data for purposes of litigation accepted by court as reliable methodology). The determination of whose conclusions are correct, however, is an issue for the trier of fact. *See Oddi v. Ford Motor Co.*, 234 F.3d 136, 146 (3d Cir. 2000) ("The analysis of the conclusions themselves is for the trier of fact when the expert is subjected to cross-examination.") (internal citation omitted).

Novartis' current position, the scientific fact is that topical Elidel use leads to concentrations of pimecrolimus in the lymph nodes and thymus sufficient to cause immunosuppression and cancer. PX 1 ¶¶ 14-15, 75-92 (Smith Rpt.); PX 3 at 8 (Kolb Rpt.); Pl. Opp. at 14-17.

Defendant's feigned confusion about the relevance of these studies (Def. Reply at 5) ignores the extensive regulatory history and concern about the concentration of pimecrolimus in lymphatic tissue following topical Elidel use.[2] Specifically, in 2005, "to further assess the biologic plausibility of lymphoma formation in local lymph nodes after topical administration," FDA and other regulatory authorities compelled Novartis to conduct the very studies from which Novartis now tries to distance itself. PX 55 at ELED-00083786 (Aug. 2, 2005 FDA letter: "[T]o further assess the biologic plausibility of lymphoma formation in local lymph nodes after topical administration, we request that you formally commit to conduct additional studies and provide data from an existing toxicology study."); *id.* at ELED-00083786 ("We request that you formally commit to conduct the studies listed below [two week dermal studies in monkeys and mice] with Elidel cream....It is recommended that pimecrolimus levels be measured in the draining lymph node, thymus, spleen and blood on days 1 and 14.").[3]

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[2] Defendant contends that Plaintiffs are simply mistaken in stating that the 2005 FDA Advisory Committee was concerned about the extent to which pimecrolimus concentrates in the lymph nodes following dermal application, incredibly asserting that Plaintiffs provided no citations on this point "because there is none available." Def. Reply at 3 n.2. Novartis is wrong on both fronts. In their Opposition, Plaintiffs cited both a memorandum from an FDA scientist to the 2005 FDA advisors, as well as the deposition testimony of the senior Novartis scientist who presented at the 2005 Advisory Committee meeting, both of which acknowledge the focus and concern about lymphatic concentrations of the drug in connection with that meeting. *See* Pl. Opp. at 26-27; PX 23 at 254:24-255:15 (Hultsch Dep.); PX 43 at ELED-00082608 (Murphy Memo).

[3] That animal studies rather than human studies were conducted to answer these questions (Def. Reply at 2) is not surprising. It simply is not morally or ethically feasible to remove the lymph nodes, spleen, thymus, or other organs from people following Elidel use to determine

Like the dermal studies themselves, the comparisons made by Dr. Smith and Dr. Kolb of the lymph node and thymus concentrations from the dermal monkey study to the oral monkey study are highly relevant. As described below, the methods undertaken and analysis completed by Plaintiffs' experts is precisely what FDA contemplated when it required the dermal studies.[4]

In the summer of 2005, when FDA asked Novartis to submit data from the 39-week monkey study (that unbelievably was not given to FDA or its advisors prior to the 2005 Advisory Committee), FDA made plain the importance of both that data and the dermal monkey data, and the purpose for which they would properly be put:

> We request that you submit to your IND the results of pharmacokinetic analsyses of tissues (lymph nodes {mesenteric, bronchial and inquinal}, spleen, thymus, ... and subcutaneous fat) that were obtained in the 9 month oral monkey toxicology study conducted with pimecrolimus. ***These data will be useful for comparison to the levels of pimecrolimus in local draining lymph nodes noted in the 2 week dermal pharmacokinetic study conducted in monkeys with Elidel cream.***

PX 55 at ELED-00083787 (Aug. 2, 2005 FDA letter).

The comparison for which FDA required these studies and data from Novartis is precisely the comparison that Dr. Smith and Dr. Kolb performed. *See, e.g.,* PX 3 at 7

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pimecrolimus tissue levels. *See* PX 5 at 123:11-12 (Smith Dep.); *see also* PX 3 at 6 (Kolb Rpt.). As Plaintiffs' experts explained, and as is evident by FDA's selection of these dermal animal models, the results from these studies are properly extrapolated to humans. PX 1 ¶¶ 35-36 (Smith Rpt.); *see also* PX 5 at 124-126 (Smith Dep.).

[4] The fallacy of Novartis' claim that FDA knew at the time of approval the extent to which pimecrolimus concentrates in the lymph nodes following topical application of Elidel (pimecrolimus cream) (Def. Reply at 3 n.2) is revealed by FDA's insistence that these two dermal absorption studies be conducted. The dermal absorption study that Novartis provided with its NDA involved a different formulation of pimecrolimus (not the Elidel formulation) that Novartis claims is of little "predictive value" in measuring absorption in humans. PX 23 at 257:1-11 (Hultsch Dep.) ("We had experimental formulation [sic] to increase the penetration of pimecrolimus through the mouse or rodent skin."). The truth remains that no dermal tissue concentration study with Elidel was provided to FDA until 2007, when Novartis finally provided its 2002 mini-pig study. Pl. Opp. at 28.

(Kolb Rpt.) (comparing concentration of pimecrolimus in lymph node and thymus in monkeys given oral pimecrolimus that developed lymphoma at every dose with those given Elidel dermally); PX 1 ¶ 102 (same); PX 5 at 256:23-257:23 (Smith Dep.); PX 7 at 331:18-332:22 (Kolb Dep.). Defendant's efforts to dismiss these studies, as well as Dr. Smith's and Dr. Kolb's conclusions from them, defies the very purpose for which the studies were designed.

B. The Cluster of Lymphoma Reports in Young Children Was Given Proper Consideration and Weight by Plaintiffs' Experts

Fighting the conclusions of its own epidemiologists and scientists, Novartis next contends that "[t]here is no 'cluster' of NHL adverse event reports in children." Def. Reply at 6. As Plaintiffs highlighted in their Opposition, Novartis scientists concluded in 2006 that there was a "cluster" of lymphoma cases in young children—a disproportionate incidence of lymphoma in children aged five and younger as compared to what would have been expected in that patient population based on sales information. Pl. Opp. at 17-18; PX 28 at ELEM-03634178 (Elidel Safety Update (Lymphoma), 7/20/06).

Contrary to Defendant's suggestion (Def. Reply at 6-9), and specifically relevant to Defendant's request for leave to submit a reply, there was nothing new about Plaintiffs' reference to a "cluster" of lymphoma cases observed in Elidel treated patients. Plaintiffs' experts specifically referenced this imbalance in lymphoma events among young children in their expert reports. Def. Reply at 6 n.5; PX 2 ¶ 21 (Smith Supp. Rpt.) ("When reviewing post-marketing reports of lymphoma of lymphoma in pimecrolimus patients from the Elidel safety database in 2006, Novartis scientists noted an imbalance of the reported cases of lymphoma in children—9 of the 34 reported lymphoma cases were

in children 5 and younger"); PX 3 at 8 (Kolb Rpt.) (noting imbalance in lymphoma cases in children).

Nor have Plaintiffs "ignore[d] another Novartis analysis, dated just nine days later" that found no cause for concern with the cluster of lymphoma cases. Def. Reply at 8. The Novartis analysis cited by Defendant actually *precedes* the analysis cited by Plaintiffs by three weeks. *Compare* Def. Reply Exh. 5 (6/29/2006 presentation) *with* PX 28 (Elidel Safety Update (Lymphoma), 7/20/06). In the later analysis relied upon by Plaintiffs and their experts (PX 2 ¶ 21 (Smith Supp. Rpt.)), Novartis acknowledged (a) the "cluster" of lymphoma cases in children age five and younger, (b) the existence of a lymphoma signal with Elidel use, and (c) the need for further investigation and studies as a result of the signal. PX 28 at ELEM-03634174, -03634180 (Elidel Safety Update (Lymphoma), 7/20/06).

Defendant's contention in Reply that its epidemiological studies exculpated Elidel is squarely contradicted by the same later-prepared document that Novartis asks the Court to ignore. There, Novartis concluded that its epidemiological studies, like its clinical studies, lacked the power to assess the risk of lymphoma in children: "the [Arellano] study did not have enough power to address the risk of lymphoma in AD patients ≤ 5." *Id.* at ELEM-03634175; *see also* PX 2 ¶¶ 2-9, 11-26 (Smith Supp. Rpt.).

As for Defendant's contention that Plaintiffs seek to prove causation by case reports, Novartis' reply simply re-plows the same ground as its initial memorandum. Def. Mem. at 17-18, 39-42; Pl. Opp. at 53-54. But Plaintiffs' experts' causation opinions do not turn on the mere occurrence of lymphoma following reports of patients' use of Elidel, as Defendant suggests. *Cf.* Def. Reply at 6-9. Plaintiffs' experts considered case

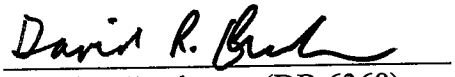
report information in the context of all the scientific information about pimecrolimus and Elidel, including the extensive studies conducted on the drug. *See* PX 1 ¶ 11 (Smith Rpt.); PX 3 at 2 (Kolb Rpt). Importantly, as stated in the *Reference Manual on Scientific Evidence* (2d ed. 2000), though "[c]ausal attribution based on case studies must be regarded with caution.... such studies may be carefully considered in light of other information available, ***including toxicological data.***" *Id.* at 475 (emphasis added). *See also Glaser v. Thompson Med. Co.,* 32 F.3d 969, 972-75 (6th Cir.1994) (finding scientifically reliable expert's opinion, based upon consideration of, *inter alia*, case reports.). Plaintiffs' experts did just that.

CONCLUSION

For the foregoing reasons, Defendant's request for leave to file a reply brief is unwarranted and should be denied.

June 17, 2008
New York, NY

Respectfully submitted,



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